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INVESTOR IN PEOPLE

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Andrew Gersey

Dated

28 October 2004

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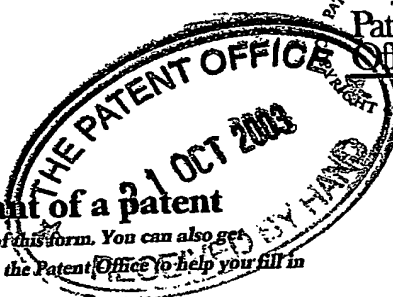
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1/77
22OCT03 E846317-4 D00041
P01/7700-0.00-0324583.4

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)



21 OCT 2003

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

REP07603GB

2. Patent application number

(The Patent Office will fill this part in)

0324583.4

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Arakis Ltd.
Chesterford Research Park
Little Chesterford
Saffron Walden
Essex

Patents ADP number (if you know it)

CB10 1XL

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

08306128001

4. Title of the invention

THE USE OF NON-OPIATES FOR THE
POTENTIATION OF OPIATES

5. Name of your agent (if you have one)

Gill Jennings & Every

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

Broadgate House
7 Eldon Street
London
EC2M 7LH

Patents ADP number (if you know it)

745002 ✓

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier UK application

Date of filing
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8. Is a Patents Form 1/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

YES

Answer YES if:

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is not named as an applicant, or
- c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

Patents Form 1/77

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form

Description 4

Claim(s) 1

Abstract

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for a preliminary examination and search (Patents Form 9/77)

Request for a substantive examination (Patents Form 10/77)

NO

Any other documents (please specify)

11. I/We request the grant of a patent on the basis of this application.

For the applicant

Gill Jennings & Every

Signature

Date 21 October 2003

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

R E Perry

020 7377 1377

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Notes

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THE TREATMENT OF PAIN

Field of the Invention

This invention relates to the use of a known compound for the treatment of pain.

5 Background of the Invention

N-methyl-D-aspartate (NMDA) receptor antagonists have been long known to exhibit anti-nociceptive effects, and a number have proven efficacy in the treatment of a number of neuropathies, including postherpetic neuralgia, central pain caused by spinal cord injury and phantom limb pain. The NMDA
10 receptor antagonist dextrorphan is disclosed for the treatment of pain in EP-A-0615749 and also, along with a number of other such compounds (including ifenprodil), in WO-A-97/14415. Unfortunately, most agents which block the NMDA receptor also induce unacceptable side-effects at analgesic doses, including memory impairment, ataxia, hallucinations and dysphoria, which
15 prohibit their widespread use.

Ifenprodil, i.e. 2-(4-benzylpiperidino)-1-(4-hydroxyphenyl)-1-propanol, selectively blocks NR2B-containing NMDA receptors in a voltage-independent and non-competitive manner (Gallagher *et al.*, 1996, J. Biol. Chem. 271(16):9603-9611) and exhibits anti-nociceptive activity in animal models of
20 acute and chronic pain (Taniguchi *et al.*, 1997, Brit. J. Pharmacol. 122, 809-812; Boyce *et al.*, 1999, Neuropharmacology 38:611-623). Ifenprodil (as ifenprodil tartrate) is commercially available as a racemic mixture of the *erythro* diastereomer.

Ifenprodil also exhibits potent alpha-1 adrenergic receptor binding
25 properties (Chenard *et al.*, 1991, J. Med. Chem. 34 (10):3085-3090) which can cause hypotension and syncope in some recipients. It is also reported by Chenard *et al.* that the *threo* isomers of ifenprodil have selectivity for the NMDA receptor over the alpha-1 adrenoreceptor.

PCT/GB03/01906 describes the utility of ifenprodil in the treatment of
30 neuropathic pain. Intranasal administration (and other routes) are described.

Summary of the Invention

The present invention is based on the discovery that ifenprodil has utility in the treatment of pain, especially non-neuropathic pain, including chronic benign and cancer pain. Accordingly, ifenprodil can be used to boost analgesia during intermittently uncontrollable episodes (breakthroughs) found in certain painful conditions. These conditions include chronic benign pain and cancer pain. The chronic benign pain states can be categorised as musculoskeletal, visceral, and headache pain and include conditions such as osteoarthritis, chronic pancreatitis, and chronic migraine. Cancer pain conditions are associated with the malignant growth of tumours both primary and metastatic in nature. The condition is thought to be associated with either pressure on normal tissue (invasion) or by the release of pro-nociceptive mediators in and around the tumour.

As suggested above, it has been thought in the past that (-)-*threo* ifenprodil has improved NMDA activity over the other enantiomers, and that this would produce a significant improvement in efficacy. Surprisingly, it has now been demonstrated that (-)-*threo* ifenprodil does not produce a significant increase in efficacy over the other enantiomers in a model of neuropathic pain. However, it has been shown that this enantiomer has lower hypotension liability (alpha1-adrenoceptor antagonism), which will improve its side-effect profile over the other enantiomers.

Description of Preferred Embodiments

Ifenprodil has two chiral centres. Any reference herein to ifenprodil should be understood as a reference to any enantiomer or mixture thereof. Any enantiomer may be substantially free of others, e.g. in an enantiomeric excess of at least 80%, preferably at least 90% and more preferably at least 95%. Similarly, any mixture of diastereomers may be substantially free of the other. The *threo* form, and in particular the (-)-*threo* form, may be preferred in certain cases; the (-)-*erythro* form may be preferred in others.

The ifenprodil may be in the form of the free base or any pharmaceutically acceptable salt, e.g. the tartrate, or in the form of a metabolite or prodrug. Such forms are known to those of ordinary skill in the art.

The active agent may be administered by, for example, the oral, topical, dermal, ocular, intravenous, intraarticular, rectal, vaginal, inhalation, intranasal, sublingual or buccal route. The amount of active ingredient that is used can be chosen by the skilled person having regard to the usual factors.

5 For use, the active agent is typically formulated, e.g. with a conventional diluent or carrier, or as a patch, as a medicament adapted to be delivered by the chosen route. Such formulations are known to those skilled in the art, and will be chosen according to the usual considerations such as the potency of the drug, the severity of the condition and the route of administration.

10 Ifenprodil is preferably administered intranasally, buccally or by any route that avoids first-pass metabolism. Indeed, nasal delivery introduces significant concentrations of ifenprodil and its isomers to NMDA receptors whilst reducing side-effects caused by the unwanted alpha-1 adrenoreceptor-binding activity. In this context, a typical daily dose is less than 60 mg, e.g. 1 to 50 mg, ifenprodil;
15 a higher dose, e.g. up to 500 mg, may be used, especially if first-pass metabolism is not avoided.

In particular, it would be of benefit to administer ifenprodil in a manner that reduced peripheral exposure to vascular smooth muscle (minimise effect on vascular tone), while maximising the concentrations in the CNS (maximise
20 analgesia). This may be done by nasal delivery, reducing systemic load, while maximising the concentration of drug in the CNS. By way of example only, a composition for intranasal delivery comprises, in addition to ifenprodil, one or more of a solubility enhancer such as propylene glycol, a humectant such as mannitol, a buffer and water. A mucoadhesive agent may also be used.

25 Ifenprodil has very poor pharmacokinetics, with very high first-pass metabolism (5% bioavailability and a short half life; $t_{1/2}$ 1 hour). Consequently, administering ifenprodil orally, to treat a chronic condition like neuropathic pain, may require high and frequent doses. Dermal administration, e.g. by the use of a dermal patch, allows chronic dosing of this compound, while avoiding first-pass
30 metabolism and so lowering the dose. Additionally, there is the potential of removing the dose from the circulation rapidly at the end of the treatment period.

It will often be advantageous to use ifenprodil in combination with another drug used for pain therapy. Such another drug may be an opiate or a non-opiate such as baclofen.

The following Example illustrates a composition suitable for intranasal delivery. In this Example, 1-10 mg ifenprodil is included in 100 μ l of:

Excipient:		%w/w	
5	Benzalkonium chloride	0.02	Preservative
	Propylene Glycol	25	Solubility Enhancer
	Mannitol	15	Humectant
	10 HNa ₂ PO ₄ (0.2M)	25.2	
	Citric Acid (0.1M)	10.0	
	Deionised water	24.6	(pH6.5 buffer)

CLAIMS

1. Use of ifenprodil for the manufacture of a medicament for the treatment of pain.
2. Use according to claim 1, for the treatment of intermittent or episodic pain experienced by a patient undergoing chronic pain treatment.
3. Use according to claims 1 or claim 2, wherein the pain is chronic benign pain.
4. Use according to claim 3, wherein the pain is related to a musculoskeletal, visceral or headache condition.
5. Use according to claim 4, wherein the condition is osteoarthritis, chronic pancreatitis or chronic migraine.
6. Use according to claim 2, wherein the pain is breakthrough pain in cancer.
7. Use according to any preceding claim, wherein the ifenprodil is in the form of either or both *threo* enantiomers.
8. Use according to claim 7, wherein the ifenprodil is (-)-*threo*-ifenprodil.
9. Use according to any of claims 1 to 6, wherein the ifenprodil is (-)-*erythro*-ifenprodil.
10. Use according to any preceding claim, wherein the medicament is for administration via a route that avoids first-pass metabolism.
11. Use according to claim 10, wherein the route is intranasal.
12. Use according to claim 10, wherein the route is dermal.
13. Use according to any of claims 10 to 12, wherein the medicament is in the form of a unit dosage containing less than 60 mg ifenprodil.
14. A composition suitable for intranasal delivery, which comprises an aqueous solution of ifenprodil, a solubility enhancer and a humectant.
15. A composition according to claim 14, wherein the ifenprodil is (-)-*threo*-ifenprodil.
16. A composition according to claim 14, wherein the ifenprodil is (-)-*erythro*-ifenprodil.

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